Boehringer Ingelheim

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Non-Interventional Study Protocol

BI Study No.:	1160.136
BI Investigational Product(s):	Pradaxa
Title:	**GLORIA – AF: G**lobal Registry on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation (Phase II/III – EU/EEA Member States)
Clinical Phase:	IV
Trial Clinical Monitor:	Telephone: Telefax:
Co- of the Steering Committee:	Telephone: Telefax: Telephone: Telefax:
Status:	Global Amendment 1
Version and Date:	**Version: 4.0** **Date: 22 October 2014**

LOCAL SIGNATURES (PRINCIPAL INVESTIGATOR OF SITE AND LOCAL CLINICAL MONITOR (CML))

Non-Interventional Study Title: **GLORIA - AF: G**lobal Registry on **L**ong-Term **O**ral Antithrombotic T**R**eatment **I**n PAtients with **A**trial **F**ibrillation
(Phase II/III – in EU/EEA Member States)

Trial Number: 1160.136

Protocol Version: 4.0

Local Clinical Monitor:

Date Name

Full name

Organization/Department

<Add other signatories if applicable.>

I herewith certify that I agree to adhere to the observational plan and to all documents referenced in the observational plan.

Principal Investigator (site):

Date Name

Full name

Organization/Department

Signed signature page is located in the electronic Clinical Trial Master File

NON-INTERVENTIONAL STUDY PROTOCOL SYNOPSIS

Name of company/Marketing Authorization Holder: Boehringer Ingelheim		**Tabulated Study Protocol**	
Name of finished product: PRADAXA			
Name of active ingredient: Dabigatran (dabigatran etexilate = prodrug)			
Protocol date: 23 March 2012	**Trial number:** 1160.136		**Revision date:** **22 October 2014**
Title of study:	**GLORIA-AF**: **G**lobal Registry on **L**ong-Term **O**ral Antithrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation. This protocol describes Phases II and III (of three phases in total) of the Registry Program in the EU/EEA* member states		
Study site(s) :	Overall up to about 680 sites (including e.g. hospitals, anticoagulant clinics, specialists and general practice settings) in up to 23 countries		
Clinical phase:	IV		
Objectives:	To investigate the patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in non-valvular atrial fibrillation (AF) patients. To collect real-world data on important outcome events of antithrombotic treatments for the prevention of stroke.		
Methodology:	International, multicenter, prospective observational study for patients with newly diagnosed non-valvular atrial fibrillation. The Registry Program will be run in three different phases. Phase I is conducted before approval of dabigatran. This protocol describes the two phases after dabigatran is approved for preventing strokes in patients with atrial fibrillation (SPAF) in participating countries (Phases II and III). The phases differ regarding the handling of the follow-up period. In Phase II (after the approval of dabigatran), there will be a cross-sectional analysis at the patient's baseline visit for all patients and a follow-up for two years for patients initially treated with dabigatran. In Phase III (given the comparability of the patient population prescribed either dabigatran or vitamin K-antagonists), new patient recruitment will be started and after the baseline visit all patients will be followed up for three years regardless of antithrombotic therapy treatment status. The baseline visit is defined as the physical visit when the patient is enrolled in the registry. Patients will either participate in Phase II or Phase III.		

Name of company/Marketing Authorization Holder: Boehringer Ingelheim		**Tabulated Study Protocol**	
Name of finished product: PRADAXA			
Name of active ingredient: Dabigatran (dabigatran etexilate = prodrug)			
Protocol date: 23 March 2012	**Trial number:** 1160.136		**Revision date:** **22 October 2014**

No. of patients:	For the EU/EEA* member states, enrollment of approximately 5,000 patients in Phase II and another 10,000 patients in Phase III is planned in total.
Diagnosis:	Patients newly diagnosed with non-valvular atrial fibrillation
Main criteria for inclusion:	Patients newly diagnosed with non-valvular atrial fibrillation (diagnosed < 3 months before patient's baseline visit) and at risk for stroke (CHA_2DS_2-VASc score of at least 1), aged 18 years or older.
Duration of follow up:	2 years for patients initiating dabigatran (Phase II); 3 years for all patients (Phase III) irrespective of anticoagulation treatment status
Outcomes*:*	Collect data on patient demographics, AF disease information, antithrombotic treatment, medical history and concomitant medication at the patient's baseline visit. In addition, compliance with the dabigatran SmPC will be examined. The patients will be followed for 2 (Phase II) and 3 years (Phase III) respectively and information such as change in antithrombotic medication since previous visit including compliance and occurrence of any outcome or safety events will be captured. In Phase II follow-up information will be collected for those patients initiating dabigatran, in Phase III for all patients.
Criteria for safety:	SAEs, ADRs and major and life threatening bleeds
Statistical methods:	Descriptive statistics for patient characteristics and treatment patterns, multivariable regression models for analyzing predictors of outcomes and for comparative analyses

* European Union/European Economic Area

FLOW CHART

OVERVIEW

Phase of registry	Baseline (time point of start of observation)	Time point 1 3 months from baseline (only phase II)	Time point 2 6 months from baseline	Time point 3 12 months from baseline	Time point 4 24 months from baseline	Time point 5 36 months from baseline
II*	V-B	V1§	V2§	V3§	V4§	
III*	V-B	-	V1	V2	V3	V4

* Individual patients will take part either in Phase II or in Phase III.
§ Should be performed only in patients initially receiving dabigatran in Phase II
V-B Baseline Visit
V Follow-up Visit

PHASE II

Data points	Baseline (V-B) time point of start of observation	Time point 1 (V1) 3 months from baseline (± 1 month)	Time point 2 (V2) 6 months from baseline (± 1 month)	Time point 3 (V3) 12 months from baseline (± 2 months)	Time point 4 (V4) 24 months from baseline (± 2 months)
	All patients	**Patients treated with dabigatran only**			
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Lifestyle factors	X				
AF disease characteristics	X				
Medical history Including current concomitant diseases	X				
Concomitant diseases (current, any change)		X	X	X	X

PHASE II continued

Antithrombotic treatment	X[1]	X[2]	X[2]	X[2]	X[2]
Selected concomitant treatment (current, any change)	X	X	X	X	X
Collect serum creatinine information (if available)	X	X	X	X	X
Outcome events (Vascular and bleeding events)[3]		X	X	X	X
Therapeutic/ diagnostic interventions		X	X	X	X
Serious adverse events [4]		X	X	X	X
Non-serious adverse drug reactions[5]		X	X	X	X
Vital Status					X

V-B Baseline Visit
V Follow-up Visit

1. Antithrombotic treatment prescribed for stroke prevention in patients with atrial fibrillation at baseline.
2. Antithrombotic treatment (current, any change) including compliance. Changes include temporary/permanent discontinuation and switch to another antithrombotic medication for stroke prevention in patients with atrial fibrillation
3. Includes outcome events defined in Section 5. Outcome events, irrespective of causal relationship with dabigatran, any antithrombotic treatment, or any other BI concomitant medication, are to be recorded on SAE or AE forms available in the registry eCRF. If the outcome event is serious and deemed to be causally related to dabigatran or any other BI drug the SAE form will be submitted in an expedited manner to the Sponsor.
4. Serious adverse events (SAEs) irrespective of causal relationship with dabigatran, any other antithrombotic treatment, or any other BI concomitant medication are to be recorded on SAE forms available in the registry eCRF. If SAE, is deemed to be causally related to dabigatran or other BI drug the SAE form will be submitted in an expedited manner to the Sponsor
5. Non-serious adverse drug reactions are defined as non-serious adverse events (AEs) with a causal relationship to dabigatran, any other BI concomitant medication, or any other antithrombotic and should be recorded on AE forms available in the registry eCRF only. Non-serious adverse events (AEs) that are NOT deemed RELATED to (i.e. caused by) dabigatran, or other BI concomitant medication, or any other antithrombotic therapy SHOULD NOT BE RECORDED in the registry eCRF.

PHASE III

Data points	Baseline (V-B) time point of start of observation	Time point 1 V1 6 months from baseline (± 1 month)	Time point 2 V2 12 months from baseline (± 2 months)	Time point 3 V3 24 months from baseline (± 2 months)	Time point 4 V4 36 months from baseline (± 2 months)
Informed consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Lifestyle factors	X				
AF disease characteristics	X				
Medical history including current concomitant diseases	X				
Concomitant diseases (current, any change)		X	X	X	X
Collect serum creatinine information (if available)	X	X	X	X	X
Antithrombotic treatment	X[1]	X[2]	X[2]	X[2]	X[2]
Selected concomitant treatment (current, any change)	X	X	X	X	X
Outcome events (Vascular and bleeding events)[3]		X	X	X	X
Therapeutic/ diagnostic interventions		X	X	X	X
Serious adverse events[4]		X	X	X	X
Non-serious adverse drug reactions[5]		X	X	X	X
Vital Status					X

V-B Baseline visit
V Follow-up Visit

1. Antithrombotic treatment prescribed for stroke prevention in patients with atrial fibrillation at baseline
2. Antithrombotic treatment (current, any change) including compliance. Changes include temporary/permanent discontinuation and switch to another antithrombotic medication for stroke prevention in patients with atrial fibrillation.
3. Includes outcome events defined in Section 5. Outcome events, irrespective of causal relationship with dabigatran, any other antithrombotic treatment or any other BI concomitant medication, are to be recorded on SAE or AE forms in the registry eCRF. If the outcome event is serious and deemed to be causally related to dabigatran or any other BI drug the SAE form will be submitted in an expedited manner to the Sponsor.
4. Serious adverse events (SAEs) irrespective of causal relationship with dabigatran, any other antithrombotic treatment or any other BI concomitant medication are to be recorded on SAE forms in the registry eCRF. If SAE, is deemed to be causally related to dabigatran or any other BI drug the SAE form will be submitted in an expedited manner to the Sponsor
5. Non-serious adverse drug reactions are defined as non-serious adverse events (AEs) with a causal relationship to dabigatran, any other antithrombotic treatment, or any other BI concomitant medication, and should be recorded on AE forms available in the registry eCRF only. Non-serious adverse events (AEs) that are NOT deemed RELATED to (i.e. caused by) dabigatran, other BI concomitant medication, or any other antithrombotic therapy SHOULD NOT BE INCLUDED in registry eCRF.

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ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
BI	Boehringer Ingelheim
CA	Competent (Regulatory) Authority
CI	Confidence Interval
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CRF	Case Report Form
CrS	Serum Creatinine Concentration
CTMF	Clinical Trial Master File
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EEA	European Economic Area
EF	Ejection Fraction
EU	European Union
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
LV	Left Ventricular

LVD	Left Ventricular Dysfunction
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
NYHA	New York Heart Association
OPU	Operative Unit
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
SAE	Serious Adverse Event
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
SPAF	Stroke Prevention in Atrial Fibrillation
TCM	Trial Clinical Monitor
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist

1. INTRODUCTION

For consistency reasons the name of the active moiety (dabigatran) of the product Pradaxa® is used throughout this document.

1.1 MEDICAL BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia and affects approximately 1-2% of the population (R03-1233). It is estimated that 6 million people in Europe and 2.7 million people in the USA suffer from AF (P10-10141, P06-08196). The lifetime risk for development of AF is one in four for those over the age of 40 years (R09-4884).

The prevalence of AF rises with advancing age, increasing from less than 1% in those below 60 years of age to nearly 20% in those 85 years of age and older (R09-4875). The overall prevalence of AF is also increasing; hospital admissions for AF have increased 60% over the past 20 years (R10-1345). The prevalence of AF is estimated to double by 2050 due to the aging of the world's population (R03-1233).

Thromboembolic complications – particularly stroke – are a major cause of morbidity and mortality in patients with AF. Most cases of stroke in patients with AF are the result of embolization of a left atrial thrombus, and particularly from the left atrial appendage. Patients with AF have a four to five fold higher risk for stroke than those without AF (R96-0252, R03-1241). Up to 15% of all strokes are due to AF and strokes in patients with AF have worse outcomes with higher mortality rates than strokes in patients without AF (R09-4892).

The risk of stroke and systemic embolisation in patients with AF is affected by patient risk factors, including a history of previous stroke or TIA, hypertension, left ventricular dysfunction (LVD), congestive heart failure (CHF), advanced age, diabetes mellitus, and coronary artery disease. Patients without any of these risk factors, i.e., lone AF, have a lower likelihood for the occurrence of stroke, thromboembolic events and stroke-related mortality (R03-1229, P06-08196, R03-1241). The classic $CHADS_2$ (Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/transient ischemic attack; see Appendix 10.1) score is a risk score that was developed to be a simple method for clinicians to assess the risk of stroke and thromboembolism in patients with AF (P06-10925). Given that the $CHADS_2$ score does not include many stroke risk factors, a modification has been developed (CHA_2DS_2-VASc score, see Appendix 10.1) to refine its predictive value for stroke and thromboembolic events (R10-5332, P10-10141).

Most cases of stroke due to AF are preventable by the use of antithrombotic therapy. A meta-analysis of all well-controlled trials demonstrated that warfarin decreased the risk of stroke/systemic embolism on average by 62% versus placebo, while antiplatelet therapy reduced the occurrence of stroke by 22% compared to placebo, although when the analysis is confined to the aspirin only trials, aspirin reduces stroke by a non-significant 19% (95% CI: -1% to 35%) compared to placebo (P07-07953, R03-1227). Oral anticoagulation with vitamin K antagonists (VKAs, e.g. warfarin) is currently the most used treatment for stroke prevention in AF patients at moderate to high-risk of stroke (P10-10141, P07-04925, P06-08196, P10-00811). However, VKAs have important limitations including a narrow

therapeutic window, an unpredictable dose–response effect, numerous drug-drug and drug-food interactions, and a slow onset and offset of action. As a result, many patients with AF do not receive VKAs but receive ASA, other antiplatelet agents, both or no antithrombotic therapy (R03-1241). Even when VKAs are used, regular anticoagulation monitoring and dose adjustments are needed to achieve effective anticoagulation with VKAs.

In a real-world setting, VKA treatment often results in INR values outside of the target therapeutic range (R10-0768, R09-1522), leaving patients at increased risk of stroke or bleeding. To address the many short comings of VKAs, multiple new oral anticoagulants are in clinical development including mainly direct thrombin inhibitors and factor Xa inhibitors (P07-08370). Dabigatran, a direct thrombin inhibitor, has been approved for the prevention of stroke and systemic emboli in patients with AF in many countries worldwide, including the United States, Canada, Japan, Australia, Korea, Mexico, Brazil, as well as EU. In the RE-LY trial, an 18,113 randomized clinical patient study (P09-11669) dabigatran (150 mg b.i.d.) has been shown to significantly reduce the occurrence of stroke (both ischemic and hemorrhagic) and systemic emboli compared to warfarin while having a comparable rate of major bleeding . In the same trial dabigatran (110 mg b.i.d.) was demonstrated to be non-inferior to warfarin for the prevention of stroke and systemic emboli while resulting in statistically significant fewer major bleeds in the same study. Importantly, both doses of dabigatran reduced the occurrence of intracranial hemorrhage in a statistically significant manner compared to warfarin (P09-11669). Of note, dabigatran has been taken up as adequate treatment alternative to VKAs in major treatment guidelines (e.g. USA, Canada, EU) during recent revisions (P11-00444, P10-14910, P10-10141, P10-14358)

With the approval of novel anticoagulants for stroke prevention in patients with AF, changes in antithrombotic treatment patterns will occur. The GLORIA-AF Registry Program is designed to collect real-world data to assess these changes.

1.2 DRUG PROFILE

Dabigatran etexilate is the orally bioavailable prodrug of dabigatran, a direct thrombin inhibitor. The prodrug (dabigatran etexilate) does not have any antithrombin activity. Following oral administration it is rapidly converted via esterases to the active moiety, dabigatran, which is a non-peptidic, potent, competitive, and reversible inhibitor of thrombin. For further information refer to the local approved label.

1.3 GLORIA-AF PROGRAM

The GLORIA-AF Registry Program consists of three phases and is an observational study. It is designed to characterize newly diagnosed patients with non-valvular atrial fibrillation at risk for stroke in different regions of the world and to describe current patterns of antithrombotic treatments selected at the patient's baseline visit. The baseline visit of each phase is defined as the visit in which the patient is enrolled into the registry. In addition, safety data and outcomes of such patients will be collected in Phase II and III of the Registry Program. Phase I is described in a separate protocol (study 1160.114; U11-1009-02) and is only related to the pre-approval time. The present protocol describes Phases II and III for the

EU/EEA-member states and is considered a substudy of the global Phases II/III of the Registry Program (1160.129; U11-1638-04).

The inclusion criteria for the different phases of the GLORIA-AF Registry Program are the same in all three phases. In each phase newly diagnosed non-valvular AF patients at risk of stroke, as characterized by a CHA_2DS_2-VASc score of at least 1 (for derivation of the score see Appendix 10.1) are planned to be included (R10-5332).

The introduction of new antithrombotic therapies for the prevention of stroke in patients with AF is changing treatment decisions. Dabigatran is the first of these new treatment choices and has been approved in an ever increasing number of countries for the prevention of stroke and systemic emboli. Therefore, Phase I of this Registry Program is conducted only in countries where dabigatran is not yet approved in order to describe the patient population and the treatments selected for stroke prevention in different regions of the world before the introduction of new oral anticoagulant therapies. Phases II and III will focus on the time after the introduction of new oral anticoagulant therapies, as defined by the approval of dabigatran in the respective country, and will also collect data on safety and outcome events of antithrombotic therapies for stroke prevention.

In the global GLORIA-AF Registry Program (Phases I-III) up to 56,000 patients are planned to be included. In all phases, data will be collected to characterize patients at the time of the baseline visit including the treatment strategy selected. In Phase I (before approval of dabigatran) no further follow-up data are collected. In Phase II (after the approval of dabigatran in a country), a two-year follow-up for newly diagnosed AF patients initiating dabigatran treatment will be added. In Phase III, which only starts after comparability has been established between important patient baseline characteristics of those initiating dabigatran and those initiating VKAs, a three-year follow-up for all patients will be conducted.

1.4 RATIONALE FOR PERFORMING THE REGISTRY PROGRAM

When evaluating new drugs, the collection of real-world data is important for studying large patient numbers that include a broad spectrum of comorbidities and co-medication use with the use of the new drug. Observational studies can provide supplementary data to data collected in randomized clinical trials which generally have stricter inclusion criteria and structured monitoring schemes.

VKAs have been shown to be effective in preventing strokes and systemic emboli in controlled clinical trials, but despite these data, they are not prescribed to as many as one half of the AF patients for whom they are indicated (R09-1482, R09-1483, R10-0756). The approval of new antithrombotic agents for the prevention of stroke in AF patients is expected to alter the use of existing antithrombotic agents and there is consequently a need to understand how the patients with different characteristics are treated in the real-world.

Also, when evaluating the safety and outcome events associated with the use of new drugs, real-world data are important to accrue larger patient numbers and broader and more heterogeneous patient populations with respect to co-morbidities and co-medication use.

The here described study (1160.136) will provide information on the utilization of dabigatran after approval and examine the compliance with the dabigatran SmPC. Specifically Phase II is designed as a Drug Utilization Study (DUS) and will allow the analysis of data collected specifically in EU/EEA member states.

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE STUDY

The rationale of the GLORIA-AF Registry Program is described in Section 1.4. Phase II and III of the GLORIA-AF Registry Program collect data on patients with newly diagnosed non-valvular AF, their treatments and outcomes in a real-world setting.

2.2 STUDY OBJECTIVES

2.2.1 Main Objective

The main objectives are:

- To investigate the patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in non-valvular AF patients
- To collect real world data on important outcome events of antithrombotic treatments for the prevention of stroke.

2.3 BENEFIT-RISK ASSESSMENT

As in any observational study, patients will be managed according to local medical practice. The choice of treatment is solely at the discretion of the participating physicians. This means there are no additional risks to patients by participating in this registry. No additional medical procedures are required, over and above those that the patient would receive if not enrolled.

Data from this Registry Program may contribute to the scientific knowledge regarding the management of patients with atrial fibrillation.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL DESIGN AND PLAN

GLORIA-AF Phase II/III is part of a global, multi-center, prospective Registry Program investigating patients with newly diagnosed non-valvular AF at risk for stroke (defined as a CHA_2DS_2-VASc stroke risk score of at least 1). Phase I (data collection before approval of dabigatran) of this Registry Program is described elsewhere (U11-1009-02). Phase II/III is outlined in three separate protocols: The present core protocol covering all global regions participating in Phase II and III of the Registry Program (1160.129, U11-1638-03) and two protocols with focus on the EU/EEA-member states (1160.136), as well as India (substudy 1160.171). The main design features within the protocols are identical and the analysis of the global study (1160.129) will also contain the data collected in patients entered in the present substudies (1160.136 and 1160.171).

Phase II, which is planned to be initiated after approval of dabigatran in the respective country consists of a baseline visit and a two-year follow-up for patients treated with dabigatran for the prevention of stroke. Thus, data on the use of dabigatran in routine clinical practice will be collected to describe how dabigatran is prescribed and used in the population of newly diagnosed non-valvular AF patients and how these factors influence important outcome and safety events. In addition, compliance with the dabigatran SmPC with regards to indication, posology, contraindications and warnings will be evaluated. The utilization of dabigatran will be assessed with regards to treatment persistence, compliance, proportion of patients discontinuing treatment and reason for discontinuation. Patients enrolled in Phase II initially receiving other oral anticoagulants than dabigatran (e.g. VKAs) or antithrombotic therapy, or no therapy for stroke prevention, will only participate in the baseline visit without participation in any subsequent follow-up visits.

Before initiation of Phase III, regular interim analyses will be conducted during Phase II on patients initiating dabigatran and those initiating VKA at the baseline visit to evaluate the similarity of patients in these two groups. These interim analyses will occur on a regional basis, based on the number of patients enrolled (approximately once or twice a year). Once comparability regarding important baseline characteristics (known risk factors for stroke and bleeding e.g. age, gender, hypertension, diabetes mellitus, prior stroke, prior transient ischemic attack, prior bleeding and concomitant medication use) of these groups has been established and the likely amount of residual channeling bias after confounder adjustment is comparatively small, Phase III will be initiated. The main measure to determine comparability of the two treatment groups regarding their important baseline characteristics will be the overlap on the propensity score, as measured by the proportion of patients in the region of overlap of the propensity score. Patients already enrolled in Phase II will complete their visit schedule as planned. Each patient enrolled into GLORIA-AF can only participate in one phase, i.e. those patients enrolled into Phase II are not eligible to participate in Phase III. In Phase III all newly diagnosed non-valvular AF patients will be followed up for three years regardless of antithrombotic therapy treatment status.

It could turn out that Phase III cannot be conducted in the EU region; i.e. if after two years of assessing baseline characteristics of dabigatran and VKA initiators in Phase II comparability

has not been achieved, which would preclude any meaningful comparisons, then one of the following three scenarios to assess long-term comparative outcomes will be pursued:

1. If substantial overlap is achieved, and comparability in Phase II is expected to be achieved within the following six months, i.e. overlap is expected to be very soon sufficient, then Phase II will be prolonged for six more months before entering Phase III.

2. If some overlap is achieved, but comparability is expected not to be achievable in Phase II within the following six months due to persistent channeling bias, then Phase III will be started and a matched analysis will be conducted, being aware of the draw back that the power could not be sufficient for all outcomes.

3. If little or no overlap is achieved, and it appears highly unlikely that comparability would be achievable even if the study were extended for a prolonged period of time as significant channeling bias persists, then a separate database study based on existing data (e.g. claims data, electronic medical records) on long-term outcomes will be initiated to ensure sufficient power within matched cohorts.

The variables that will be considered for matching in scenario 2 and 3 will consist of a subset of those that were used for the assessment of comparability. Their choice will be based on the strength of the association of those variables with the outcome under study and the learnings from the interim results. At least age and gender will be matching variables. In addition, scores derived from those variables (e.g. the estimated propensity score) could be considered as a matching variable.

The study described in this protocol will collect data in up to 23 European countries (for planned participating countries see Appendix 10.3) in up to about 680 sites and is planned to involve as many as 2,000 investigators. It is planned to enroll approximately 5,000 patients in Phase II and another 10,000 patients in Phase III.

The planned registry period is from July 2011 to June 2020, which covers the total expected duration of Phase II and III.

Enrollment into Phase III of the global study will end after the overall enrollment goal has been met, or by June 2017, whichever comes first. Individual regions may end earlier depending on recruitment.

3.1.1 Administrative structure of the study

Steering Committee

A Steering Committee will provide scientific leadership for the planning and conduct of all phases of the Registry Program. It will be composed of experts in cardiology, vascular medicine, neurology and epidemiology with one Chair and Co-Chair as well as representatives of the Sponsor. A charter describing the tasks and responsibility of the committee will be developed. Membership in the Steering Committee may change over time for various reasons.

Operations Committee

The study conduct will be overseen by an Operations Committee (OC), consisting of the Chair, Co-Chair, the epidemiologist of the Steering Committee and representatives of the sponsor. The Operations Committee will oversee the execution of the Registry Program and, in conjunction with the SC, facilitate the publications. Membership in the Operations Committee may change over time. In Phase II, the OC will evaluate the results of the periodic analyses of the patient baseline characteristics which will determine the initiation of Phase III of the Registry Program. In Phase III, the OC will continue to evaluate the results of periodic interim analyses to compare the baseline characteristics of patients initiating dabigatran or VKAs. The number of members can be changed if warranted. A charter of the Operations Committee will be developed.

The OC will meet regularly, based upon the volume of work. Meetings will generally be by teleconference or web-conference. Face-to-face meetings may occasionally be held if there is a necessity.

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The registry includes newly diagnosed non-valvular AF patients at risk for stroke. This permits comparison of treatment initiators and facilitates correct adjustment for predictors of treatment rather than for consequences of treatments (intermediates). In addition, this allows for the assessment of treatment hazards over time and avoids the inclusion of prevalent users of anticoagulants who are potentially healthier and less susceptible to adverse outcomes (so called “VKA survivors”) compared to new users (R11-2308).

Furthermore, the assessments of channeling bias in Phase II will allow for collecting longitudinal data on patients starting dabigatran and VKA only after they are deemed comparable regarding their important baseline characteristics, and thus reduce the potential for biased comparisons in Phase III. However, if comparability of baseline characteristics is insufficient, alternative approaches will be followed to assess long-term outcomes (see section 3.1).

3.2.1 Potential for bias and confounding

Selection bias

Selection bias may occur on two different levels: The site level and the patient level. If sites where dabigatran is most used differ systematically with respect to patients or routine procedures from sites in which it is less used, the between-site difference would lead to noncomparability between dabigatran patients and others, even if no clinician accounted for patient characteristics in his or her decision to use the product.
To minimize selection bias at the site level, the goal is to have participating centers reflect a (country specific) balance between general practices, specialist offices, community hospitals, university hospitals, outpatient care centers and anticoagulation clinics. Basic characteristics

of sites that did not participate will be summarized.
Selection bias at the patient level might occur if for example, sites preferentially reported "interesting" cases to the Registry, and particularly if they did so differently for initiators of dabigatran and VKAs. To minimize selection bias at the patient level, consecutive patients from each site who meet entry criteria of this Registry Program are expected to be invited to participate in the registry.

Consecutive enrollment of patients to avoid selection bias should be emphasized. As participation in another international registry is an exclusion criteria for entry into the study (please refer to section 3.3.3), parallel enrollment in another international registry on the use of oral anticoagulation in AF in the same department should be avoided, as otherwise consecutive enrollment would be challenging. In addition, it should be ensured that both dabigatran and VKAs are available at participating sites or that availability for both treatment options is foreseen in the near future. In the latter case, information on treatment availability has to be documented.

Loss to follow up

All efforts will be made to minimize loss to follow up in patients with a pre-planned follow up (such as patients initiating dabigatran in Phase II and all patients in Phase III), particularly in the assessment. Also, patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated.

Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if dabigatran would be more often prescribed to higher risk patients compared to other treatments, higher incidences of outcome events were then expected in the dabigatran group. The potential for channeling bias will be reduced due to the two phase design of the Registry Program and will be assessed throughout the study. The assumption is that some channeling bias may occur in the immediate post-approval period, but will not persist; therefore periodic assessment of choice of treatment in relation to the patients' important baseline characteristics will allow appropriate timing of initiating Phase III. However, if comparability of baseline characteristics is insufficient, alternative approaches will be followed to assess long-term outcomes (see section 3.1).In order to control for potential channeling bias after approval of dabigatran, regular assessments will be conducted, i.e. patients initiating VKAs and dabigatran will be assessed regarding the comparability of important patient baseline characteristics (known risk factors for stroke and bleeding, e.g. age, gender, hypertension, diabetes mellitus, prior stroke, prior transient ischemic attack, prior bleeding and concomitant medication use). Further comparisons of drugs may be added in order to reflect the possible approval of other new oral anticoagulants. This will be performed within regions. Details of the decision process for triggering the start of Phase III will be described in the Statistical and Epidemiological Analysis Plan (SEAP).

Depletion of susceptibles and healthy user/ adherence bias

Depletion of susceptibles occurs, when persons most at risk for an event suffer the event early on in therapy, so that cohorts ascertained later in therapy have a lower prevalence than such at risk patients. In the absence of a direct measure of susceptibility, depletion of susceptibles manifests itself as an apparently declining risk with the passage of time. Other common reasons for a risk that decline with time elapsed since initiation of therapy include metabolic adaptations that diminish the effect of the product (tachyphylaxis) and the prescriber's acquisition of skill in managing the drug for a particular patient. Whatever the origin, when the risk of an outcome varies over time especially when the risk is higher just after initiating therapy and declines thereafter, the comparison of prevalent users and incident (new) users will be biased, because long-time users will be less likely to manifest the outcome of interest. In addition, there is potential healthy user / adherence bias, which is that patients who use a drug or are adherent with treatment are more likely to be healthier in general (e.g. have other healthy behaviors) than patients who are non-user/non-adherent. The effects of changes in risk with time and adherence will be mitigated through the use of initiator cohorts and will be assessed through an intention to treat sensitivity analysis. Only newly diagnosed AF patients initiating antithrombotic treatment at baseline will be included throughout the Registry Program. To account for time varying risks, estimates of cumulative risks will be calculated.

Information and recall bias

Information bias can occur for example, due to selective under-reporting of already established and known adverse effects for a known product (VKA) as compared to a new product (dabigatran), or vice versa. A standardized data collection form will be used for assessing exposure and AEs (see Section 6). Medical charts will also be reviewed by site staff and during CRA monitoring visits. These standardized procedures for data collection are intended to minimize such biases. Recall bias may be caused, e.g. if visits are separated by long time intervals and patients forget certain information (e.g. use of over-the-counter medications). It can be reduced by associating questions with specified time intervals (e.g. how often did you take this co-medication during the last 7 days?).

Confounding

As in any observational study, confounding may affect the estimation of association between drug exposure and outcome of interest and statistical techniques such as adjustment for covariates, stratified analyses, matching, etc. can be used to correct for these. But as only major confounders for selected research questions can be captured, residual (unmeasured) confounding may remain.

3.3 SELECTION OF POPULATION

Regarding the consecutive enrollment of patients, please refer to Section 3.2.1.

3.3.1 Main diagnosis for study entry

Patients with newly diagnosed non-valvular AF (documented by 12 lead ECG, ECG rhythm strip, pacemaker/ICD electrocardiogram, or Holter ECG) less than 3 months before the patient’s baseline visit will be included. Each patient must be at risk for stroke with one or

more risk factors, as defined by a CHA_2DS_2-VASc stroke risk score of at least 1 (see Table 10.1: 2)

3.3.2 Inclusion criteria

1. Age ≥18 years at enrollment

2. Male or female patient (or legally acceptable representative) willing and able to provide written informed consent

3. Patient newly diagnosed (< 3 months prior to baseline visit) with non-valvular AF. Documentation of AF by 12 lead ECG, ECG rhythm strip, pacemaker/ICD electrocardiogram, or Holter ECG (duration of AF episode at least 30 seconds) needed for all enrolled patients.

4. Patient must have a CHA_2DS_2-VASc score of at least 1 (see Table 10.1: 2). This requires the presence of at least one of the following risk factors:

    a. Congestive heart failure (NYHA Class 2 or greater) or moderate to severe LV systolic dysfunction (e.g. LV EF ≤ 40%)

    b. History of hypertension or systolic blood pressure >160mmHg

    c. Diabetes mellitus

    d. History of stroke, transient ischemic attack, or systemic embolism

    e. Vascular disease defined as prior myocardial infarction, peripheral artery disease, complex aortic plaque

    f. Age ≥ 65

    g. Female gender

Although AF diagnosis is a baseline requirement, patients are not required to have an ongoing AF episode at the time of entry into this Registry Program.

3.3.3 Exclusion criteria

1. Presence of any mechanical heart valve, or valve disease that is expected to require valve replacement intervention (surgical or non-surgical) during the course of the assigned registry phase.

2. Patients who have received more than 60 days of VKA treatment in their lifetime prior to the patient's baseline visit

3. AF with a generally reversible cause (e.g., cardiac surgery, pulmonary embolism, untreated hyperthyroidism)

4. Patient's life-expectancy is expected to be less than one year at the time of potential enrollment as assessed by the investigator

5. Patients with a medical condition other than atrial fibrillation for which chronic use of an oral anticoagulant (for example, a VKA) is indicated

6. Current participation in any clinical trial of a drug or device

7. Current participation in an international registry on the use of oral anticoagulation in AF

8. Patient was enrolled in any other phase of the GLORIA-AF Program.

9. Patient with no further follow-up possible with enrolling investigator during planned study period (such as anticipated relocation).

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

A patient can be withdrawn from the registry for the following reasons:

- A patient or legally accepted representative withdraws consent
- The patient was erroneously included in the Registry Program
- Participation in another international drug study or registry on the use of oral anticoagulation in AF
- Participation in a clinical trial with a drug or device
- Any other reason as agreed to by the Investigator and the BI Clinical Monitor

The Clinical Monitor at BI or BI's designees must be immediately notified if a patient is discontinued prematurely for any of the reasons cited above. The Investigator will indicate on the End of Study form page the reason/s for discontinuation. If a patient discontinues the study prematurely, another follow-up assessment should be performed if possible (unless the reason for discontinuation is erroneous enrollment of the patient into the study at baseline), and data should be entered on the eCRFs of the next planned visit.

Patients should NOT be discontinued from the registry study due to an SAE or a non-serious AE unless the patient withdraws their consent to participate in the study. Ongoing information on adverse events is important data that should be collected on all patients who are being followed up, for the full duration of the follow-up period.

3.3.4.2 Discontinuation of the study by the sponsor

Boehringer Ingelheim reserves the right to discontinue the study overall (cf. Section 3.1) or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular study site,

2. Emergence of any efficacy/safety information that could significantly affect continuation of the study or any other administrative reasons,

3. Violation of GCP, the protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the registry.

4. It could turn out that Phase III might not be conducted; e.g. if after two years of assessing baseline characteristics of dabigatran and VKA initiators in Phase II comparability has not been achieved, which would preclude any meaningful comparisons, a comparative data collection will then not be started (cf. Section 3.1). If during Phase III the comparability of VKA and dabigatran initiators with regard to important baseline comparisons is not maintained and no other unbiased comparisons of interest are feasible then Phase III may be stopped.

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

A specific registry site could be terminated for the following reasons:

- Failure of the Investigator to enroll patients into the registry at an acceptable rate;
- Failure of the Investigator to comply with pertinent regulations;
- Knowingly submitting false information from the site to the Sponsor, CRO and/or regulatory bodies

4. TREATMENTS

4.1 PRESCRIBED TREATMENTS TO BE OBSERVED

In this observational (i.e. non-interventional) study no specific treatment is mandated and no treatment will be withheld from patients. The choice of antithrombotic agent and dosing should be according to local clinical practice and is at the discretion of the treating physician.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

All concomitant medications are prescribed based on the underlying medical condition and upon the discretion of the treating physician.

4.3 TREATMENT COMPLIANCE AND COMPLIANCE WITH SmPC

Compliance with antithrombotic therapy for stroke prevention is measured over a period of time and will be assessed by derivation of the following variables on a patient-level:

- Proportion of filled prescriptions reported by the patient relative to written prescriptions by the physician for this patient (based on CRF data from each planned visit; objective measure).
- Proportion of days with compliant medication intake (based on reference period as specified in the CRF from each planned visit, subjective measure)

Compliance with the SmPC of dabigatran will be evaluated by analysing different patient characteristics such as age, weight, hepatic disease, renal function, further stroke and bleeding risk factors and concomitant medications in relation to the prescription of dabigatran (including dose selection)

5. VARIABLES AND THEIR ASSESSMENT

5.1 OUTCOMES

5.1.1 Outcome measures

The patient's baseline characteristics including the antithrombotic treatment selected at the baseline visit will be captured.

During the follow-up of patients initiating dabigatran in Phase II and all patients in Phase III, respectively, antithrombotic treatment will be recorded. In Phase II the utilization of dabigatran will be assessed with regards to treatment persistence, compliance, and changes in antithrombotic therapy (e.g., dose adjustments, proportion of patients discontinuing treatment and reason for discontinuation). In addition compliance with the dabigatran SmPC with regards to indication, posology, contraindications and warnings will be evaluated. In Phase III the utilization of antithrombotic therapy will be collected for all antithrombotic therapies prescribed for the prevention of stroke.

The following events are considered important clinical outcomes (definitions are provided in Section 5.1.2). Additional events of interest might be included based on new information that could become available during the course of the registry and based on results obtained by the described main analysis:

- Stroke (hemorrhagic, ischemic, uncertain classification)
- Transient ischemic attack (TIA)
- Systemic embolism
- Pulmonary embolism
- Myocardial infarction
- Life-threatening bleeding events
- Major bleeding events (including life-threatening bleeding events; see definition in Section 5.1.2)
- All cause death
- Vascular death

In addition, the following two composite endpoints will be analyzed:

- Stroke, systemic embolism, myocardial infarction, life-threatening bleeding events and vascular death

- Stroke, systemic embolism, myocardial infarction and vascular death (vascular composite endpoint)

5.1.2 Assessment of outcome measures

Compliance

Compliance with antithrombotic therapy prescribed for the prevention of stroke is measured over a period of time and will be assessed by derivation of the following variables on a patient-level:

- Proportion of filled prescriptions reported by the patient relative to written prescriptions by the physician for this patient (based on CRF data from each planned visit; objective measure).
- Proportion of days with compliant medication intake (based on reference period as specified in the CRF from each planned visit, subjective measure)

Treatment persistence

Treatment persistence will be assessed as time until permanent discontinuation of the treatment (number of days or years).

Compliance with the dabigatran SmPC

Compliance with the dabigatran SmPC will be captured by collecting the appropriate variables, such as renal function, stroke and bleeding risk factors, concomitant medications and diseases at baseline and during follow-up.

- Compliance with SmPC Indication: All patients included in the study are non-valvular atrial fibrillation (NVAF) patients at risk for stroke. The AF diagnosis and all risk factors for stroke will be collected at baseline, so that compliance with the SmPC indication for dabigatran can be analysed.
- Compliance with SmPC Contraindications: To investigate, if a contraindication to dabigatran is present, such as severe renal or hepatic impairment, impairment of hemostasis and contraindicated concomitant medications the respective variables will be recorded at baseline and during the follow up of the patients.
- Compliance with SmPC Posology: All factors relevant for dose selection, such as age, concomitant drugs and renal function (by computing the creatinine clearance based on collected serum creatinine, if a blood test was performed) will be analysed.
- Compliance with SmPC Warnings: The treatment with dabigatran will be recorded at each visit including interruptions for outcome events (including major bleeds), procedures and other events which necessitate treatment interruptions (e.g. major trauma). If known by the investigator also information on bridging strategies will be collected. Whether the physician is compliant to the warnings section of the dabigatran SmPC, can be investigated using data captured on dose selection, comedications, comorbidities including factors that increase the bleeding risk and important outcome events.

The following definitions apply and should be used as a guide when reporting a thrombotic event:

Stroke:

Stroke is an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. The stroke is categorized as ischemic or hemorrhagic or uncertain classification (based on CT or MR scanning or autopsy). Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin scale (see Table 10.1:4) at discharge from hospital and/or at 3-6 months later (if available).

Transient ischemic attack (TIA):

TIA is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction (P11-00444).

Systemic embolism:

Systemic embolism is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), typically documented by angiography, surgery, scintigraphy, or autopsy.

Pulmonary embolism:

- A patient has to fulfil the following criteria:
    1. Typical symptoms or signs (e.g., dyspnoea, left or right sided chest pain worsening on respiration, etc.) suggestive of pulmonary embolism

AND at least one of the following two criteria:

2. CT pulmonary angiography demonstrating an intraluminal filling defect in segmental or more proximally located pulmonary arteries

3. High probability ventilation - perfusion lung scan, i.e. at least segmental perfusion defect at perfusion scan with normal ventilation at ventilation scan

- The definition of pulmonary embolism is also met if a patient fulfils at least criteria 2) or 3) above.

Myocardial infarction:

- In patients **not** undergoing PCI or CABG: A patient has to fulfil either the criteria:

    - Development of significant Q-waves in at least 2 adjacent ECG leads.

    Or at least 2 of the following three criteria:

- Typical prolonged severe chest pain of at least 30 min
- ECG changes suggestive of myocardial infarction including ST-changes of T-wave inversion in the ECG).
- Elevation of troponin or CK-MB[1] to more than upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level.

- After PCI (within 24 h)
  Elevation of troponin or CK-MB[1] to more than 3xULN or, if CK-MB is elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves[2] in at least two adjacent ECG leads.
- After coronary artery bypass grafting (within 72 h)
  Elevation of CK-MB[1] to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves[2] in at least two adjacent ECG leads.

[1] Total CK if CK-MB was not available [2] A new Q-wave with a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads

Major bleeding, defined as meeting one or more of the following criteria (R11-1250, P11-05406):

- Overt bleeding associated with a reduction in haemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells
- Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding
- Life-threatening bleeding

Life-threatening bleeding, defined as meeting one or more of the following criteria:

- Symptomatic intracranial bleed
- Reduction in haemoglobin of at least 50 grams per liter
- Transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents
- Necessitated surgical intervention
- Fatal bleeding

Deaths

Deaths will be classified as being: vascular (including bleeding); non-vascular, due to other specified causes (e.g., malignancy), or unknown cause, when cause is not known.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

Please refer to safety related outcome events as described in section 5.1.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse Event (AE):

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with the drug of interest.

Serious Adverse Event (SAE):

- results in death,
- is immediately life-threatening,
- results in persistent or significant disability/incapacity,
- requires or prolongs patient hospitalization,
- is a congenital anomaly/birth defect or
- is to be deemed serious for any other reason representing a significant hazard, which is comparable to the aforementioned criteria.

The basis for judging the causal relationship between the product of interest and the adverse event is described below.

(Serious) Adverse Drug Reaction (S)ADR:

If an adverse event has been deemed by the investigator to have a causal relationship with a drug, it is regarded as an adverse drug reaction.

Causality assessment:

The expression “Reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. Medical judgment should be used to determine the causal relationship, considering all relevant factors, including pattern of reaction, temporal relationship, positive de-challenge or re-challenge and/or confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship to the antithrombotic drug given for stroke prevention should be recorded in the eCRF.

- Yes: There is a reasonable causal relationship between the drug administered and the AE.

- No: There is no reasonable causal relationship between the drug administered and the AE.

Intensity of event:

Mild:	Awareness of a sign or symptom which is easily tolerated
Moderate:	Discomfort enough to cause interference with usual activity
Severe:	Incapacitating or causes inability to work or undertake usual activities

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs including blood pressure, pulse rate, ECG, physical examination, and laboratory tests will be only then recorded as AEs if they are not associated with an already reported AE, symptom or diagnosis, and the investigational drug is either discontinued, reduced or increased, or additional treatment is required, i.e. concomitant medication is added or changed.

Worsening of Pre-existing Conditions:

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF. If serious, an SAE form should also be completed.

5.2.2.2 Adverse event and serious adverse event reporting

During the course of the Registry Program, i.e. from signing the informed consent onwards until up to 6 days after the end of the last follow-up visit, all SAEs, Outcome Events described in Section 5 of this protocol and certain non-serious AEs are to be collected, documented, and reported by the Investigator on the appropriate forms (SAE or AE forms) available in the EDC systems.

For patients who undergo a baseline visit only, with no follow-up visits, only events that occur between the signing of the consent form and the conclusion of the baseline visit need to be reported.

Reporting will be done according to the specific definitions detailed in the “Adverse Event Reporting” section of this protocol and according to the instructions provided thereafter.

All SADRs continuing after the end of the Registry Program need to be followed up until the patient recovered or the event is sufficiently followed up.

Any SADR related to dabigatran or any other BI drug the Investigator may become aware of in the period up to 6 days after completion of the last follow-up visit must also be collected in the SAE form available in the EDC system and reported according to the specific definitions detailed in the “Adverse Event Reporting” section of this protocol and followed up until the patient recovered or the event is sufficiently followed up.

BI has set up a list of AEs which are defined to be always serious. This means that these events are, by their very nature, always defined as serious even if an occurrence of one of

these events does not technically meet the usual criteria for seriousness (for example, stroke). In order to support the investigator with identification of these "always serious adverse events", a list of these events is provided in the EDC system. In addition, if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description of the event. If the event description is correct, then it must be reported by the investigator as an SAE in an expedited fashion the same as for other SAEs.

ADVERSE EVENT REPORTING:

- All SAEs and Outcome Events irrespective of causal relationship with dabigatran or any other drug will be collected on SAE or AE forms in the EDC System. In other words, all SAEs are collected, and all Outcome Events are collected irrespective of drug intake or causality assessment.

- In rare occasions, if an Outcome Event was non-serious, it will be collected on the AE form in the EDC system (instead of the SAE form).

- Non-serious AEs with a causal relationship to any antithrombotic drug including dabigatran or VKA, or any BI drug are collected on AE forms in the EDC System. Non-serious AEs that are deemed NOT related to (i.e. caused by) dabigatran, VKA, any other antithrombotic therapy, or to BI concomitant medication SHOULD NOT be entered in the EDC System. For example, a non-serious AE deemed related to a non-BI diabetes drug would not be entered into the EDC system at all. Similarly, a non-serious AE which is not deemed related to any drug would not be entered into the EDC system at all**.**

- Non-serious AEs which are deemed related to a BI drug must be reported to BI within seven days of the site learning of the AE.

For SADRs and causally related Outcome Events the Investigator should provide all information requested on the SAE form immediately (i.e. within 24 hours or next business day) of becoming aware of the event. The EDC System is configured in such a way that the SAE form will be forwarded to the Sponsor automatically upon electronic signature by the Investigator, or within 24 hours of the initial data entry, whichever is shorter. For back up purposes (e.g. if computer problems or a blackout of the internet connection do not allow a timely completion of the SAE form in the EDC System) a hardcopy of the SAE form will also be available in the Investigators Site File (ISF) and should be forwarded to the fax number provided in the ISF immediately. In case the hardcopy had to be used, it has to be ensured that the SAE form in the EDC system is completed afterwards in addition.

With receipt by the site of any further information to the events, a follow-up SAE report has to be completed immediately (within 24 hours or next business day). If the SAE form is updated with new or corrected information, a follow-up report is created and forwarded to the Sponsor upon submission by the Investigator. If the hardcopy has to be used this has to be updated manually and faxed immediately.

For BI products a link to website: boehringer-ingelheim.com is provided in the EDC System. Further guidance on how to navigate on BI's websites is provided in the ISF. In addition, the Investigator should refer to the local pharmacopoeia.

Reporting of drug exposure during pregnancy:

In rare cases pregnancy might occur. Once a female subject has been enrolled into the Registry Program and was exposed to either dabigatran or any other BI drug, the Investigator must report immediately any drug exposure to the Sponsor to the fax number provided in the ISF for SAE reporting. The outcome of the pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form (available for download in the EDC system) is to be completed. If pregnancy is associated with an SAE, both the SAE form available in the EDC System and the Pregnancy Monitoring Form should be completed and forwarded/submitted to the sponsor. The ISF will contain the Pregnancy Monitoring Form (Part A and Part B) and it is also available for download in the EDC System.

5.3 OTHER

Not applicable

5.4 APPROPRIATENESS OF MEASUREMENTS

The measures conducted within this Registry Program reflect the current real-world approach regarding clinical practice across the different countries.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Recommended timing of assessments is presented in the Flow Charts for Phases II and III of the Registry Program, and summarized in Table 6.1: 1. The time intervals given for each of the scheduled visits serve as indicators as to when the contact to the patient as well as the respective data entry into the registry data base (eCRF) should take place. All assessments are intended to be performed during one visit (cf. Flow Chart), e.g.at the time of a routine, scheduled appointment. The information from each visit should be entered as quickly as possible into the eCRF after patient contact and may only be delayed in case medical record abstraction is required e.g. to capture INR data, which may not be immediately available if not performed at the site.

Due to the observational design, the dates for follow-up visits are only recommendations. The visit windows allow for flexibility. Collection of data in the study should be managed during routine practice visits (i.e., the visits should not be conducted via telephone.). In the exceptional case that a physical visit is not possible e.g. due to the transient inability of a patient to attend the practice, this particular visit can be conducted via telephone with the patient. However, all efforts should be made to ensure that the following visit is again a physical visit.

The sites selected for participation in the study are invited to all phases of the Registry Program described in the present protocol. However, additional sites may be opened to accelerate recruitment for Phase II or Phase III. The site staff will be asked to provide data regarding site and physician characteristics, including:

- type of facility (e.g. general practice, specialist office, community hospital, university hospital, out-patient care center, anti-coagulation clinic)
- specialty of the treating physician/investigator
- size of clinic/practice
- numbers of newly diagnosed AF patients during last 12 months

Table 6.1: 1 Schedule of data collection* (cf. Flow Chart)

	Baseline	**3 months (± 1 month)**	**6 months (± 1 month)**	**12 months (± 2 month)**	**24 months (± 2 month)**	**36 months (± 2 month)**
Phase II**	X	X§	X§	X§	X§	-
Phase III**	X	-	X	X	X	X

* Due to the observational design, the dates for follow-up visits are only recommendations. Visit windows allow for flexibility. Collection of data in the study should be managed during routine practice visits
**Patients will take part either in Phase II or in Phase III
§ Follow-up in patients prescribed dabigatran (at baseline) only

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Assessments in Phase II of GLORIA-AF

The following data will be collected for all patients in Phase II at enrollment, for the purposes of cross-sectional analyses. Follow-up assessments will be done only in patients who receive dabigatran. The baseline visit is defined as the physical visit when the patient is enrolled in the registry.

Assessments at Baseline:

- Date of baseline visit
- Date of informed consent
- Date of diagnosis of non-valvular AF
- Inclusion/exclusion criteria
- Demographic data, including: date of birth (month and year), gender, weight, height (calculated BMI) and race
- Blood pressure, heart rate and serum creatinine (if available)
- Information regarding AF
    - Symptomatic, minimally symptomatic, asymptomatic
    - Type (paroxysmal, persistent, permanent)
    - Previous cardioversion, ablation, pacemaker, implantation, use of LAA occlusion device and/or left atrial procedures
- Medical history (including current concomitant diseases)
- Selected concomitant treatments (antihypertensive, heart failure and anti-arrhythmic therapies, metabolic and anti-inflammatory) and other selected drugs.
- Antithrombotic treatment selected including start date (all antithrombotic therapies, for stroke prevention as well as other indications).

Assessments at the Follow-up Visits (cf. Flow Chart):

- Date of follow up visit
- Type of follow up visit
- Concomitant diseases (current, any change)
- Serum creatinine to be recorded (if available)
- Antithrombotic treatment (current, any change (start and stop dates) including compliance, reason for change; including interruptions of antithrombotic treatment due to therapeutic/diagnostic interventions)
- Selected concomitant treatment (current, any change)
- Outcome events as listed in Section 5.1
- Information is recorded on any therapeutic/diagnostic interventions that occur as part of regular follow-up
- All serious adverse events judged as related or unrelated to any BI drug (see section 5.2.2.2)
- Non-serious adverse events judged as related to any antithrombotic therapy including dabigatran or to any BI drug (see section 5.2.2.2)

- Vital status (only at last follow-up visit)

Only for those patients who are prescribed dabigatran the 3-, 6-month, 12-month (1 year) and 24 months (2 year) follow-up visits should be conducted. All follow-up visits and assessments should be conducted even if the patient discontinues treatment with dabigatran or switches to another antithrombotic treatment for AF.

If a patient prematurely discontinues from the registry, a follow-up assessment should be performed at time of study discontinuation if possible, and the end of study eCRF completed.

6.2.2 Assessments in Phase III of GLORIA-AF

In Phase III a baseline assessment is performed for all patients, identical to the baseline assessments for Phase II as described in Section 6.2.1.

Follow-up assessments will be done for ALL patients (i.e. irrespective if antithrombotic treatment status).

Assessments at Follow-up Visits:

Follow-up visits: 6-month, 12-months (1 year), 24-months (2 years) and 36-months (3 years) after Baseline visit.

- Date of follow-up visit
- Type of follow-up visit
- Concomitant diseases (current, any changes)
- Serum creatinine to be recorded (if available)
- Antithrombotic treatment (current, any change (start and stop dates) including compliance, reason for change; including interruptions of antithrombotic treatment due to therapeutic/diagnostic interventions)
- Selected concomitant treatment (current, any change)
- Patients receiving VKAs: the last three INR values and dates performed, from files and if necessary by contacting INR clinics, hospitals, etc.
- Information about VKA therapy such as location of INR testing (physician's office, freestanding lab, home testing), including discontinuations and re-starts, dates, reasons for changes, etc.
- Outcome events as listed in Section 5.1
- Information is recorded on any therapeutic/diagnostic interventions that occur as part of regular follow-up
- All serious adverse events judged as related or unrelated to any drug (see section 5.2.2.2)
- Non-serious adverse events judged as related to any antithrombotic therapy including dabigatran, or to any BI drug (see section 5.2.2.2)
- Vital status (only at last follow-up visit)

If a patient prematurely discontinues from the registry, a follow-up assessment should be performed at time of study discontinuation if possible, and the end of study eCRF completed.

6.2.3 End of study and follow-up period

For early Discontinuation:

- Date of Registry discontinuation
- Reason for Registry discontinuation
- Vital status

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details of all analyses will be provided in the statistical and epidemiological analysis plan (SEAP).

7.1 STATISTICAL DESIGN - MODEL

Phase II and III of this prospective, multi-center observational study consist of a cross-sectional collection of baseline data for newly diagnosed non-valvular AF patients and a two and three years follow-up period, respectively. Within Phase II only patients who receive dabigatran for AF treatment at baseline will be followed longitudinally. Within Phase III all patients will be followed longitudinally and the groups of newly diagnosed AF patients started on VKA and dabigatran, respectively, are assumed to be comparable in terms of important baseline characteristics due to the design of the Registry Program.

The newly diagnosed non-valvular AF population will be described using a cross-sectional approach.

For Phase II, longitudinal data on dabigatran treated patients will be summarized descriptively.

In Phase III, given that initiators of dabigatran and VKAs are comparable regarding important baseline covariates, the comparison between dabigatran and VKAs in terms of the composite endpoint in Phase III will be based on multivariable regression models using time-to-event methodology. However, if comparability of baseline characteristics is insufficient, alternative approaches will be followed to assess long-term outcomes (see section 3.1).

Due to the variable time at risk in this registry setting, analysis of outcome events will focus on incidence rates and cumulative risk using Kaplan-Meier curves or other life-table techniques.

7.2 NULL AND ALTERNATIVE HYPOTHESES

!"# $%$&#($ ")# %* $&+, %-,#).($+%'(/ ,$"0here is no (confirmatory) hypotheses testing foreseen in a strict statistical sense. 2'(/1,#, ()# 0#,3)+4$+.#' '($")# +'3/"0+'5 46(/"#, ('0 3%'*+0#'3# +'$#).(/, *)%7 ,$($+,$+3(/ 7%0#/, ",#0 *%) #84/%)($+.# 4")4%,#,9

However, the main and further objectives are defined in Section 2. Additional research objectives can be described in the SEAP.

7.3 PLANNED ANALYSES

Analyses will be performed by Boehringer Ingelheim or Boehringer Ingelheim's designees.

A final analysis and a report of Phase II will be prepared once the data collection of Phase II is completed, the data are cleaned and the database is locked. The final analysis of Phase III

(if conducted) will be done after Phase III is completed, the data are cleaned and the database is locked. It will be described in a combined report of Phases II and III together.

Analyses on a country level might be performed in addition, once the report or interim report of phase II (or phase III) is available or if required due to regulatory requirements.

The main analysis population will consist of all eligible patients (i.e. all patients fulfilling all inclusion criteria and no exclusion criteria) and the analysis will focus on the antithrombotic treatment choice for stroke prevention at baseline.

Summary statistics for continuous variables will include the N, mean, standard deviation, minimum, Q1 (lower quartile), median, Q2 (upper quartile), and maximum value; tabulations of categorical variables will present all possible categories and will display the number of observations per category as well as percentages. All estimates will be presented with 95% confidence intervals.

Additionally, similar primary and other analyses as described for the total Registry Program also will be conducted using data from only patients enrolled in the EU/EEA member states covered by this protocol (1160.136).

7.3.1 Main analyses

A) Patient characteristics influencing choice of antithrombotic treatment for stroke prevention at baseline

Demographics and baseline characteristics (including specifically stroke/bleeding risk scores ($CHADS_2$, CHA_2DS_2 -VASc and HAS-BLED, see Appendix 10.1)) will be summarized descriptively for all eligible patients by antithrombotic treatment choice for stroke prevention at the baseline visit.

The antithrombotic treatment choice for stroke prevention at the baseline visit (e.g. none, VKAs, ASA, clopidogrel, dabigatran, etc.) will be described.

Potential channeling bias between patients initiating dabigatran and VKA at the patient's baseline visit will be explored using comparisons of important baseline characteristics (known risk factors for stroke and bleeding, e.g. age, gender, hypertension, diabetes mellitus, prior stroke, prior transient ischemic attack, prior bleeding and concomitant medication use) between the two groups at regular intervals during Phase II and Phase III. This includes the generation of two-way comparisons for each of the baseline characteristics (dabigatran versus VKA) and calculation of a propensity score using multiple regression models to predict the probability of treatment choices (see also interim analyses 7.3.4).

B) Important outcome events (Phase II only)

Incidence rates and cumulative risks over time since initiation with 95%-confidence intervals for important outcome events (see Section 5.1.) will be calculated within the dabigatran cohort. In addition these analyses will be done stratified by chronic antiplatelet treatment at baseline. The analysis will be based on all eligible patients initiating dabigatran for stroke

prevention at baseline. Patients who discontinue initial dabigatran treatment for stroke prevention permanently will be censored at date of last drug intake + 3 days or at first intake of other relevant chronic antithrombotic treatment for stroke prevention, whatever comes first (unless the event occurred prior to the time of censoring). A patient is considered to have permanently stopped initial dabigatran treatment if other relevant chronic antithrombotic treatment is initiated for stroke prevention or otherwise dependent on the duration of a treatment interruption (thresholds of treatment interruption duration and other details will be described in the SEAP).

C) Important outcome events / analysis of composite endpoint of stroke, SEE, vascular death, MI, life-threatening bleeds (Phase III only)

Incidence rates and cumulative risks with 95%-confidence intervals for the composite endpoint and for the individual components of the composite endpoint will be calculated. This analysis will be repeated within subgroups. Examples of subgroup variables are age, gender and stroke and bleeding risk factors. In addition the calculation of incidence rates and cumulative risks will be done stratified by chronic antiplatelet treatment. If the patients initiating dabigatran treatment for stroke prevention at baseline are comparable (in terms of important baseline characteristics) to those initiating VKA treatment, incidence rates within these two groups will also be reported.

The analysis will be based on antithrombotic treatment choice prescribed for stroke prevention at baseline and all eligible patients. Patients who discontinue initial antithrombotic treatment for stroke prevention permanently will be censored at date of last drug intake + 3 days (for dabigatran and non VKA treatments) and +6 days (for VKA treatment or combinations of VKA with other antithrombotic treatments) or at first intake of other relevant chronic antithrombotic treatment for stroke prevention, whatever comes first (unless the event occurred prior to the time of censoring). A patient is considered to have permanently stopped initial antithrombotic treatment for stroke prevention, if other relevant chronic antithrombotic treatment is initiated for stroke prevention or otherwise dependent on the duration of treatment interruption (details will be described in the SEAP).

7.3.3 Safety analyses

The safety analysis will include all patients enrolled in Phase II and Phase III with planned follow up (i.e. only patients starting on dabigatran in phase II). Statistical analysis and reporting of AEs will be descriptive in nature, will be based on BI standards and will focus on adverse drug reactions (related to antithrombotic therapy for stroke prevention). No hypothesis testing is planned.

Occurrences of AEs will be analyzed relative to the number of patients treated and additionally relative to observed patient-years (i.e. time at risk). The safety analysis will be based on the concept of treatment emergent adverse events. Patients will be analyzed according to the antithrombotic treatment for stroke prevention they have received at the time of the event. If no current antithrombotic treatment for stroke prevention is administered then events occurring within a washout period of three days (in case of dabigatran and non VKA treatments) or six days (in case of VKA treatment or combination of VKA with other antithrombotic treatment) after discontinuation of antithrombotic treatment will be assigned to the last treatment given. This washout period will also be included as time at risk for derivation of total patient-years. Adverse events that deteriorate under treatment will also be considered as 'treatment emergent'. Adverse events occurring prior to first intake of antithrombotic treatment for stroke prevention prescribed at baseline, during periods without any antithrombotic treatment (excluding washout period) or after the individual 2 year (Phase II) or 3 year (Phase III) follow-up visit dates (excluding washout periods) will not be considered treatment emergent events and will not be included in summary tables.

The safety analyses will include the following parameters:

- ADRs (related to antithrombotic therapy for stroke prevention)
- ADRs (related to antithrombotic therapy for stroke prevention) leading to discontinuation of antithrombotic treatment
- Serious ADRs (related to antithrombotic therapy for stroke prevention)
- Deaths
- SAEs

Additionally, an analysis of ADRs restricted to those events which are related to the antithrombotic treatment for stroke prevention initiated at baseline will be performed.

Systematic collection of vital signs and laboratory parameters is not planned.

7.3.4 Interim analyses

Analysis of baseline characteristics will be performed during the conduct of Phase II and Phase III on a regular basis in order to assess comparability of VKA and dabigatran treatment cohorts and potential other treatment groups. The comparability of the patient baseline characteristics prescribed either VKAs or dabigatran will be evaluated at regular intervals (e.g. approximately twice per year, dependent on the recruitment). For these analyses appropriate statistical methods, which will include propensity scores will be used to assess channeling bias. The decision to start with Phase III will be made by the steering committee (SC) and will be based on the interim analyses performed in context of the global study Phase II and III (1160.129, U11-1638-03),

Additional types of interim analyses will be performed in context of the global study (1160.129), including regional analyses of Phase II / Phase III baseline data.
At the time of those analyses or afterwards, additional interim analyses on the baseline and/or follow-up data for the EU/EEA patients (i.e. all patients included in 1160.136 study) might be done (including e.g. respective analysis on compliance with SmPC).

7.4 HANDLING OF MISSING DATA

In order to assess the effects of lost to follow-up patients, percentages of dropouts and reason for loss to follow-up will be summarized in patients with a pre-planned follow up (such as patients initiating dabigatran in Phase II and all patients in Phase III). In addition baseline characteristics of patients who were lost to follow-up in comparison to patients with a complete follow-up will be described.

Any reasonable attempt will be undertaken to ensure completeness of data collection in this registry. Imputation might be performed dependent on amount and distribution of missing values.

7.5. RANDOMISATION

Not applicable.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to recruit approximately 5,000 patients in Phase II and approximately 10,000 patients in Phase III.

The number of patients included in Phase II and duration of enrollment is not driven by a formal sample size calculation but is primarily dependent on the availability of eligible patients treated with dabigatran and on the presence of channeling bias.

Throughout the Registry Program the aim is to describe characteristics of the newly diagnosed non-valvular AF population in treatment regimen cohorts and overall by calculation of estimates and confidence intervals for relevant attributes. The following paragraphs describe the statistical precision (width of 95% confidence interval) when estimating prevalence and incidence.

Estimates for proportions/prevalences (Phase II-III)

Categorical attributes will be estimated with the following precision (i.e. width of descriptive 95% confidence interval), depending on sample size and prevalence of the attribute:

Table 7.6: 1 Width of 95% confidence interval dependent on attribute prevalence and sample size

Attributes prevalence [%]		Sample size (for subgroup or overall) 500	1000	2000	4000	5000	10000
5	Expected n	25	50	100	200	250	500
	95%-CI width	4.03	2.81	1.96	1.38	1.23	0.86
10	Expected n	50	100	200	400	500	1000
	95%-CI width	5.46	3.82	2.68	1.88	1.68	1.19
20	Expected n	100	200	400	800	1000	2000
	95%-CI width	7.2	5.05	3.55	2.5	2.24	1.58
30	Expected n	150	300	600	1200	1500	3000
	95%-CI width	8.21	5.77	4.06	2.86	2.56	1.81
40	Expected n	200	400	800	1600	2000	4000
	95%-CI width	8.77	6.17	4.34	3.06	2.74	1.93
50	Expected n	250	500	1000	2000	2500	5000
	95%-CI width	8.94	6.29	4.43	3.12	2.79	1.97

For Phase II a total sample size of 5,000 patients allows an estimation of a population attribute with a precision of less than 2.8% (i.e. width of 95% CI).

For subgroups which consist of at least 500 patients; this allows an estimation of a population attribute within the subgroup with a precision of approximately 8.9% (i.e. width of 95% CI).

For Phase III a total sample size of 10,000 patients allows an estimation of a population attribute with a precision of less than 2.0% (i.e. width of 95% CI).

Estimates for incidence rates (Phase II-III):

Estimates and confidence intervals for incidence rates (interpreted on a descriptive level) will be computed. For Phase II it is estimated to recruit approximately 2,500 patients from EU/EEA member states in the dabigatran treatment cohort whom are followed up for up to 2 years. Assuming a total treatment discontinuation and lost to follow-up rate of 25% per year a

total of approximately 3,802 patient-years in patients from EU/EEA member states starting dabigatran will be observed.

When observing 3,802 dabigatran patient years, we will observe at least one patient with an event (ADR, MBE, stroke/SEE, etc), if the underlying incidence rate for this event is 0.079 occurrences per 100 patient years or above with a power of 95%. If we do not observe any event within the 3,802 patient years, it can be excluded with 95% confidence that the underlying true event rate is above 0.079 per 100 patient years in the population.

Based on the recent RE-LY trial (warfarin, dabigatran), it is expected that the incidence rates for stroke/SEE and MBE will be in a range of 1 to 3 per 100 patient years in the total population. The width of the two-sided 95% confidence interval of the population depends on the obtained estimate from the sample of 3,802 patient years; the following table illustrates this relationship:

Table 7.6: 2 95% Confidence intervals based on different scenarios for observed event rates (based on 3,802 patient years)

Observed event rate per 100 patient years	Lower 95% CI for event rate per 100 patient years	Upper 95% CI for event rate per 100 patient years
1	0.70773	1.372465
2	1.575877	2.503151
3	2.474761	3.603743

The calculation of confidence intervals is based on the method described in Hahn, Meeker (section 7.2.2; using χ^2-quantiles). (R12-3048)

As an example, assume that the event rate for stroke per 100 patient years is 1, i.e. we observe ˜38 strokes within the 3,802 patient years. The two-sided 95% confidence interval for the population incidence rate per 100 patient years is 0.71 to 1.37. Thus it can be excluded with 95% confidence that the true rate of strokes per 100 patient years is above 1.37 in the population.

For Phase III, for treatment group cohorts which initially consist of at least 2,000 patients, approximately 4,019 patient-years will be observed within the treatment regimen cohort. This approximation is based on the assumptions of a total treatment discontinuation and lost to follow-up rate of 25% per year and an individual follow-up of three years. Therefore, due to the longer individual follow-up in Phase III and thereby the longer observation time per patient, estimates of incidences based on treatment regimen cohorts which initially consist of 2,000 patients will have approximately the same precision as described above (for 2,500 patients in Phase II).

95% confidence intervals will be calculated for several outcome events. Therefore, it can be expected that false positive significant differences may arise, i.e. a treatment regimen cohort may appear by chance with a lower or a higher incidence rate for specific outcome events or for the composite endpoint variable; consequently, results have to be interpreted with care.

8. INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

Phase II and III as part of the Registry Program will be conducted in accordance with the protocol, the principles of Good Clinical Practice (GCP), the Declaration of Helsinki as of October 2008 (R10-1167), guidelines for Good Epidemiological Practice (R10-4560), Good Pharmacoepidemiologic Practice (R09-0182), "Registries for Evaluating Patient Outcomes: A User's Guide" (R10-4561), relevant BI Standard Operating Procedures (SOPs) and local regulations.

The Investigator should inform the Sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments. All protocol amendments must be documented, dated and signed by all appropriate signatories. Local, country specific amendments may be generated.

Prior to patient participation in Phase II or III of the Registry Program, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to International Committee on Harmonization GCP and to the regulatory and legal requirements of the participating country. The patient should be given appropriate time to consider if he/she accepts to participate in the Registry Program.

Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the Investigator as part of the Registry Program.

A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by Boehringer Ingelheim's designees, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit (monitoring) of Phase II or III of the Registry Program may be conducted by the Sponsor or Sponsor's designees. The quality assurance auditor must be provided access to all medical records, the investigator's registry-related files and correspondence, and the informed consent documentation that is relevant to this Registry Program.

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic CRFs (eCRFs) will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data, or complex cross-form verifications such as lab result deviations across visits. Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate. Source data verification (SDV) will be performed at-sites-identified by a risk-based approach outlined in the monitoring plan, as needed.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

8.3 RECORDS

All of the clinical data and site/investigator characteristics will be captured via a web-based EDC System. The Investigator site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. The Investigator will approve the data using an electronic signature: (21 CFR Part 11 compliant).

Patients must not be identified on the eCRF by name. Appropriate coded identification (i.e., patient number) must be used. The Investigator must make a separate confidential record of these details (patient identification code list) to permit identification of all patients enrolled in Phase II or III of the Registry Program in case follow-up is required. Likewise, any supporting documentation must be redacted of any patient identifying information, and the patient ID number clearly written on the documents.

The clinical data the Investigator entered into the EDC System together with all data changes made will be available to the Investigator for download at the end of Phase II or III of the Registry Program. The Investigator will be responsible for retaining all records pertaining to the Registry Program as specified in the appropriate contract.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available. For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

The Investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's representative(s) and or designee(s), auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on-site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1 and in the Monitoring Plan.

8.4 PROCEDURES FOR REPORTING ADVERSE EVENTS

8.4.1 Time windows

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. For the BI product(s) this is the Company Core Data Sheet (CCDS) i.e. the applicable Summary of Product Characteristics (SPC). The documents can be referred to via a link to website: boehringer-ingelheim.com provided in the EDC System and guidance document on how to navigate on BI's websites provided in the ISF.

8.4.2 Documentation of adverse events and patient narratives

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of Phase II or III of this Registry Program is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study needs to be available for inspection on request by the participating physicians, by the IRB / IEC competent health authorities and the sponsor and/or its representatives and/or designees.

The data collected in the eCRFs will be transferred to the database via the Internet through secure web-sites.

8.6 COMPLETION OF STUDY

The EC/competent authority in each participating EU member state needs to be notified about the end of the study (last patient out) or early termination of the registry.

8.7 PUBLICATION POLICY

It is the joint task of the Operations and the Steering Committee to facilitate publications and/or presentations of data from Phase II or III of this Registry Program. Authorship will be determined jointly by the OC, SC and the Sponsor. The rights of the Operations Committee, of the Investigators and of the Sponsor with regards to publication of the result of Phase II or III of this Registry Program are described in the individual contracts and in the SC and OC charters. Any publication on the Phase II or III of this Registry Program though must be consistent with the BI publication policy and guided by the current version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journals (ICMJE). As a general rule, no national study results should be published prior to finalization and publication of the overall results of the interim and final analyses of the respective phase.

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10. APPENDICES

10.1 RISK SCORES FOR AF PATIENTS

Data collected at the baseline visit will be used to generate the following scores for use in the respective analysis:

Table 10.1: 1 $CHADS_2$ Stroke Risk Score

CHADS2 components	**Points**
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Prior cerebral ischemia (i.e., stroke, TIA)	2
Maximum score	6

$CHADS_2$ score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack and 1 point each is assigned for age 75 years or older, hypertension, diabetes, or clinical heart failure or impaired left ventricular systolic function (generally interpreted as an ejection fraction $\leq 40\%$). A $CHADS_2$ score of 0 identifies patients at low stroke risk, a score of 1 to 2 identifies patients at moderate stroke risk, and a score greater than 2 identifies patients at high stroke risk (P06-10925).

Table 10.1: 2 CHA_2DS_2-VASc Stroke Risk Score

$CHA_2DS_2VAS_c$ score	
Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	**Clinically relevant non-major risk factors**
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40 %) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VAS_c (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

* myocardial infarction, complex aortic plaque and PAD

The CHA_2DS_2-VASc risk score is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a hypertension, diabetes, cardiac failure, vascular disease and female sex. On the basis of the risk strata defined in previous guidelines, a CHA_2DS_2-VASc score of 0 corresponds to "low risk", a score of 1 corresponds to "intermediate risk", and a score of 2 or more corresponds to "high risk" (R10-5332).

Table 10.1: 3 HAS-BLED Bleeding Risk SCORE

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	**Clinical characteristic**	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum score		**9**

Hypertension is defined as uncontrolled systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Within this study information on "Labile INRs" is not captured for any of the patients (neither for VKA-treated nor for non-VKA-treated patients), therefore this component will be set to 0 for all patients. Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA the value for 'labile INRs' will not be assessed. Further details will be given in the SEAP.

A HAS-BLED score of ≥3 indicates 'high risk' for AF patients to develop a bleed and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin (R10-6394).

Table 10.1:4 Modified Rankin Scale (mRS)

Definition of disabling stroke by modified Rankin Scale:	
Grade 0:	no symptoms at all
Grade 1:	no significant disability despite symptoms; able to carry out all usual duties and activities
Grade 2	slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
Grade 3:	moderate disability: requiring some help but able to walk without assistance
Grade 4:	moderate severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
Grade 5:	severe disability: bedridden, incontinent, and requiring constant nursing care and attention.
Grade 6:	dead

10.2 CREATININE CLEARANCE

The serum creatinine clearance will be calculated according to Cockroft-Gault:

Cl_{cr} (ml/min) = (140-age)*weight (kg) * GF

72 * Scr (mg/dL)

Cl_{cr} = Creatinine clearance

$S_{cr}Cr_s$ = Serum creatinine

(when serum creatinine is given in µmol/L, divide the value by 88.4)

GF = Gender correction factor (0.85 for women and 1.00 for men)

10.3 LIST OF PLANNED PARTICIPATING COUNTRIES

Table 10.3: 1 List of planned participating countries

Planned Participating Countries (EU and/or EEA)				
Austria	Finland	Latvia	Slovenia	Ukraine
Belgium	France	Lithuania	Spain	
Bulgaria	Germany	Norway	Sweden	
Croatia	Greece	Poland	Switzerland	
Czech Republic	Hungary	Portugal	Turkey	
Denmark	Ireland	Romania	The Netherlands	
Estonia	Italy	Slovakia	UK	

Note: Not all planned countries will participate, and it is possible that some countries not listed here will later be added.

Summary of High Level Changes from Version 3 dated 23 March 2012

Number of global amendment		*1*
Date of CTP revision		*22 October 2014*
EudraCT number		*NA*
BI Trial number		*1160.136*
BI Investigational Product(s)		*None*
Title of protocol		***GLORIA-AF: G****lobal Registry on* ***L****ong-Term* ***O****ral Anti-thrombotic T****R****eatment* ***I****n P****A****tients with* ***A****trial* ***F****ibrillation (Phase II/III)*
To be implemented only after approval of the IRB/IEC/Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB/IEC/ Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section changed #1		*Title Page and subsequent sections in the protocol (eg. Table of Contents, Synopsis, Signature Page)*
Description of change		*Change heading from "Post Marketing Surveillance Study Protocol" to Non-interventional Study Protocol"*
Rationale for change		*Updated corporate SOP and new template for observational studies.*
Section changed #2		*Title Page*
Description of change		*Enter name and contact information of current TCM (.)*
Rationale for change		*New TCM*
Section changed #3		*Flow Chart Phase II and Phase III*
Description of change		*Added to Flow Chart Phase II and Phase III, information if available on serum creatinine and any therapeutic/ diagnostic interventions. Clarify Non-Serious Adverse Event Reporting in Phase II to match that of phase III. Any Non-Serious Adverse events related to any antithrombotic use will now be recorded on eCRFs in Phase II as*

Number of global amendment		*1*
		well as Phase III.
Rationale for change		*Include serum creatinine and therapeutic/diagnostic interventions. Clarify and streamline Non-Serious Adverse Event reporting.*
Section changed #4		*1.1 Medical Background*
Description of change		*Clarify countries where dabigatran has been approved.*
Rationale for change		*Section required updating.*
Section changed #5		*3.1 Overall Design and Plan*
Description of change		*Add substudy 1160.171 to be conducted in India. Add that interim analyses will occur on a regional basis based on the number of patients enrolled (approximately once or twice a year).*
Rationale for change		*India was added as part of a separate substudy (1160.171) for administrative and logistical reasons only.* *Timing of interim analysis was formerly approximately every 6 months, but the timing of analysis is more driven by adequate number of patients enrolled.*
Section changed #6		*3.1 Overall Design and Plan*
Description of change		*Clarify planned number of countries, sites and patients in the EU. Clarify planned registry period will be from July 2011 to June 2020. Enrollment will end after the overall enrollment goal has been met, or by June 2017, whichever comes first.*
Rationale for change		*Clarification of registry period and to indicate possibility for some regions to end early.*
Section changed #7		*3.2 Discussion Of Study Design, Including The Choice Of Control Group(s)*
Description of change		*Clarification that if comparability of baseline characteristics is insufficient, alternative approaches will be followed to assess long-term outcomes*
Rationale for change		*Clarification of assessments of long-term outcomes.*
Section changed #8		*3.2.1 Potential for bias and confounding* *3.3 Selection of Population*
Description of change		*Consecutive enrollment of patients to avoid selection bias is emphasised and parallel enrollment in another international registry should be avoided. Sites should also be selected wherever possible if both dabigatran and VKA is available.*

Number of global amendment		*1*
Rationale for change		*Clarification to minimize potential for bias by confirming consecutive enrollment and ensure selected sites have capability to enrol both dabigatran and other VKAs are available.*
Section changed #9		*3.3.3 Exclusion Criteria*
Description of change		*Exclusion criterion #6 is changed from "Current participation in any clinical trial of an experimental drug or device" to "Current participation in any clinical trial of a drug or device"*
Rationale for change		*Participation in any clinical trial of a drug or device, including those of marketed drugs or devices, should exclude the patient from this registry because patient's treatment would likely be influenced by participation in the trial.*
Section changed #10		*3.3.4.1 Removal of individual patients*
Description of change		*It will no longer be true that a patient may be removed from the study due to persistent failure of the patient to comply with the protocol and study procedures. Removal of a patient due to violation of exclusion criterion #6 (participation in a clinical trial with a drug or device) is revised to be consistent with the new wording of exclusion criterion #6. Removal of a patient due to violation of exclusion criterion #7 (Participation in another international registry on the use of oral anticoagulation in AF) is clarified by adhering to the language used in Section 3.3.3. The "Patient Disposition CRF page" is now referred to by its proper designation, "the End of Study form." A reminder is inserted that "If a patient discontinues the study prematurely, another follow-up assessment should be performed if possible (unless the reason for discontinuation is erroneous enrollment of the patient into the study at baseline), and data should be entered on the eCRFs of the next planned visit." A reminder is inserted that patients should not be discontinued from the study due to adverse events.*
Rationale for change		*The conditions under which a patient may be removed from the study are clarified to be consistent with the principles of a registry study and with changes made elsewhere in the protocol.*
Section changed #11		*5.1.1 Outcome Measures*
Description of change		*There are some changes to the list of Outcome*

Number of global amendment		*1*
		measures. "Non vascular death" and "Death of unknown cause" have been removed from follow-up. Two composite endpoints will now be analysed. *Clarification that information on all antithrombotic medications will be collected irrespective of indication.*
Rationale for change		*Clarification*
Section changed #12		*5.1.2 Assessment of outcome measures*
Description of change		*"Fatal bleeding" removed from "Major bleeding, defined as meeting one or more of the following criteria" and placed under "Life-threatening bleeding, as defined as meeting one or more of the following criteria".*
Rationale for change		*Clarification*
Section changed #13		*5.2.2.1 Assessment of Adverse Events*
Description of change		*Added section on 'Worsening of Pre-existing Conditions'*
Rationale for change		*Added to be in conformance to the drug safety SOP 001-MCC-40-002*
Section changed #14		*5.2.2.2 Assessment of Adverse Events* *AE reporting instructions were clarified and addition of an always serious list was added.*
Description of change		*Inclusion of BI list of AEs which are defined to be always serious. This means that these events are, by their very nature, always defined as serious even if an occurrence of one of these events does not technically meet the usual criteria for seriousness (for example, stroke).* *Unified instructions for AE reporting for Phases II and III. It was determined that it was not necessary to have separate instructions for Phase II and III. The only change is clarification that the requirement to report non-serious AEs which are deemed related to an antithrombotic other than dabigatran applies to both Phase II and III.* *Further clarification is provided to the investigator about what reporting functions are performed automatically by the system and what are the responsibilities of the site personnel. It is also clarified that Non-serious AEs which are deemed related to a BI drug must be reported to BI within seven days of the site learning of the AE.*
Rationale for change		*Streamlined and simplified instructions for*

Number of global amendment		*1*
		reporting of SAEs and non-serious AE and required reporting timeline for NSAE reporting of related events was clarified.
Section changed #15		*6.1 Visit Schedule and Table 6.1: 1 Schedule of data collection*
Description of change		*It is clarified: Due to the observational design, the dates for follow-up visits are only recommendations. The visit windows allow for flexibility. Collection of data in the study should be managed during routine practice visits (i.e., the visits should not be conducted via telephone). In case a physical visit is not possible e.g. due to the transient inability of a patient to attend the practice, the visit can be conducted via telephone.*
Rationale for change		*Clarification that patients are not mandated to come into the clinic for visits during specified time windows, and clarification that visits by phone can exceptionally occur when needed.*
Section changed #16		*6.2.1 Assessments in Phase II of GLORIA-AF*
Description of change		*For Assessments at Baseline, add "(if available)" after "Blood pressure, heart rate and serum creatinine", and add "Antithrombotic treatment selected including start date (all antithrombotic therapies, for stroke prevention as well as other indications)." For Assessments at the Follow-up Visits, add "Type of follow up visit,", "Serum creatinine to be recorded (if available)," and "Information is recorded on any therapeutic/diagnostic interventions that occur as part of regular follow-up". The bullet point regarding the reporting of SAEs is simplified to say "All serious adverse events judged as related or unrelated to any BI drug." (Reference to dabigatran or other BI drugs is removed since it is unnecessary and potentially confusing.) The bullet point regarding the reporting of non-serious AE is changed to say, "Non-serious adverse events judged as related to any antithrombotic therapy including dabigatran, or to any BI drug (see Section 5.2.2.2)." (The inclusion of any antithrombotic therapy is clarified to be consistent with the simplifications made in Section 5.2.2.2.)*

Number of global amendment		*1*
		Also, add clarification that a follow-up assessment should be performed at time of study discontinuation if possible, and the end of study eCRF completed.
Rationale for change		*Clarifications that information pertaining to vital signs, creatinine clearance and any therapeutic procedures is only recorded if the information is available. The protocol does not mandate any additional procedures or lab tests to be performed by the physician above those which are part of the patient's normal medical care. The type of follow-up visit (in person or via telephone) is recorded. The descriptions of SAE and non-serious AE information collected is modified to conform with the modifications made to section 5.2.2.2.* *Clarification around follow-up and eCRF completion upon early discontinuation was added.*
Section changed #17		*6.2.2 Assessments in Phase III of GLORIA-AF*
Description of change		*This is for Phase III. Same as for changes for follow-up visits for Phase II as described above for section 6.2.1.*
Rationale for change		*Same as for section 6.2.1.*
Section changed #18		*7.1 Statistical Design - Model*
Description of change		*Same as for changes noted in section 3.2 as described above.*
Rationale for change		*Same as for section 3.2.*
Section changed #19		*7.3 Planned Analyses*
Description of change		*Analyses on a country level might be performed in addition, once the report or interim report of phase II (or phase III) is available or if required due to regulatory requirements.*
Rationale for change		*This statement helps to clarify that the final analysis of country data should only be done after interim analysis.*
Section changed #20		*7.3.1 Main Analysis* *A) Patient characteristics influencing choice of antithrombotic treatment for stroke prevention at baseline*
Description of change		*Examples of known risk factors for stroke and bleeding added, e.g. age, gender, hypertension, diabetes mellitus, prior stroke, prior transient*

Number of global amendment		*1*
		ischemic attack, prior bleeding and concomitant medication use.
Rationale for change		*Clarification of important baseline characteristics.*
Section changed #21		*7.3.1 Main Analysis* *B) Important outcome events (Phase II only)*
Description of change		*Clarification that outcome event analyses will be stratified generally by relevant chronic antiplatelet therapy.*
Rationale for change		*Clarification of analyses of important outcome events in Phase II. Previously, it was to be stratified by chronic antiplatelet use for the AF indication but information on antithrombotic treatment will be collected independent of indication as the effect of antithrombotic treatment is also independent of indication.*
Section changed #22		*7.3.1 Main Analyses* *C) Important outcome events/ analysis of composite endpoint of stroke, SEE, vascular death, MI, life-threatening bleeds (Phase III only)*
Description of change		*By adding the term "relevant" it was indicated that not each change in e.g. antiplatelets use would necessarily result in censoring of a patient for the main analysis.* *The stratified analysis of incidence rates and cumulative risk by antiplatelets use at baseline was removed from the protocol.*
Rationale for change		*Clarification in terms of the planned analysis*
Section changed #23		*7.3.2 Further Analyses* *D) Important outcome events/ analysis of composite endpoint of stroke, SEE, vascular death, MI, life-threatening bleeds/ analysis of composite vascular endpoint/ exploration of factors impacting safety and effectiveness of dabigatran (Phase III only)* *F) Potential side effects of antithrombotic treatments for stroke prevention*
Description of change		*D) Add that a multivariable Cox regression model and further covariates will be implemented in groups where comparability is obtained to explore the association between baseline characteristics and specific outcome events. Hazard ratios will be reported. The analysis will be based on antithrombotic treatment choice prescribed at baseline, where comparable. Add*

Number of global amendment		*1*
		that patients followed in Phase III will be assessed for important outcome events and composite vascular endpoint and that interaction terms impacting safety and effectiveness will be included in multivariable regression models. Clarification that the regression model will include antiplatelet use. Remove that the incidence rates for the dabigatran and VKA groups by subgroup variables will be assessed. F) Add that further country-specific analyses might be done.
Rationale for change		*Clarification of analysis plan multivariable regression models and to include further country specific analyses.*
Section changed #24		*7.3.3 Safety analyses*
Description of change		*Add "prescribed at baseline"*
Rationale for change		*Clarification that adverse events occurring prior to first intake of antithrombotic treatment for stroke prevention; is referring to antithrombotic treatment prescribed at baseline.*
Section changed #25		*7.3.4 Interim Analyses*
Description of change		*Details of specific additional interim analyses were removed.*
Rationale for change		*The additional types of interim analyses will be performed in the context of the global study 1160.129 and are further described there.*
Section changed #26		*Table 10.1:3, Text following HAS-BLED Bleeding Risk SCORE Table*
Description of change		*Specify definitions of "Hypertension" and "Labile INRs"*
Rationale for change		*Clarification*
Section changed #27		*Appendix 10.3 List of Planned Participating Countries*
Description of change		*Added additional planned countries to the table consistent with 1160.129 protocol. Also added note that "Not all planned countries will participate, and it is possible that some countries not listed here will later be added."*
Rationale for change		*Update and clarification on country participation.*
Section changed #28		*All sections*
Description of change		*Typographical and grammatical errors corrected throughout the document.*
Rationale for change		*Correction as required to fix minor wording errors, spacing, and punctuation.*

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		13 Nov 2014 20:51 CET
Approval-Therapeutic Area		14 Nov 2014 07:41 CET
Approval-Team Member Medicine		14 Nov 2014 14:59 CET
Approval-Other		14 Nov 2014 17:48 CET
Approval- of Global Epidemiology		15 Nov 2014 17:04 CET
Author-Trial Statistician		18 Nov 2014 09:03 CET
Author-Trial Clinical Monitor		18 Nov 2014 14:57 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed